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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,370	10/03/2001	Randall K. Holmes	33,383-00	8568

270 7590 05/25/2006

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,370	HOLMES ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/15/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-17,28-37 and 39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,28-37 and 39-44* is/are rejected.

7)☒ Claim(s) *3,29 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/16/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13-17, 28-37,39-44 are pending.
Claim 1 and all claims dependent therefrom have been amended and claim 15 have been amended.

Allowable Subject Matter

1. Claim 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Additionally, claim 29 is rejected under 35 USC 112, second paragraph set forth below. Obviating the rejection under 35 USC 112, second paragraph could define allowable subject matter.
2. Claims 3 and 44 define over the prior art of record and are therefore allowed, but are rejected under 35 USC 112, second paragraph set forth below. Obviating the rejection under 35 USC 112, second paragraph could define allowable subject matter.

Information Disclosure Statement

3. The information disclosure statement filed February 15, 2006 has been considered.

Rejections Maintained/Response to Arguments

Response to Declaration by Ms. Mary E. Bak

4. The Declaration submitted by Ms. Mary E. Bak, filed on February 15, 2006 has been considered but is ineffective to overcome the New Matter objection to the Specification.

5. The Declaration of Ms. Mary E. Bak states that the Declaration was submitted in compliance with 37 C.F.R. 1.57(f).

6. It is the position of the examiner that the instant Specification does not qualify for incorporation by reference under 37 C.F.R. 1.57(f) in light of the fact that the effective filing date of **the instant Specification was not filed on or after September/October 21, 2004** when the new rules became effective. Therefore, a Declaration and an amendment compliant with a rule that was not available to the instant Application, constitutes a ineffective Declaration.

7. While the examiner previously mentioned 37 CFR 1.57(f), this section of the MPEP was quoted for providing guidance that No New Matter should be submitted.

8. The examiner that stated that the rules for incorporation by reference of essential material should be based upon the rules in effect prior to September/October 2004 provided additional discussion. A statement that the amendatory material **consists of the same material incorporated by reference in the referencing application,** should be made of record. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167(CCPA 1973). This statement was not made in the Declaration submitted by Ms. Bak and therefore was/is found ineffective to overcome the outstanding New Matter rejection of record.

The amendment filed July 12, 2004 is still objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO 1.

The amino acid sequence was improperly incorporated by reference to International Application WO93/13202. No original descriptive support in the instant Specification could be for the amino acid sequence of SEQ ID NO 1. Applicant in claims 15 and 16 claims the embodiments disclosed in WO93' in combination with Applicant's mutation set forth in at least claim 1. Therefore the Specification has been amended to recite narrative that is New Matter. Applicant is required to cancel the new matter in the reply to this Office Action or submit an effective Declaration for the proper incorporation by reference of essential subject matter.

9. The rejection of claims 1-11, 13-17, 28-37, 39-44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter is traversed on the grounds that:

a. an effective Declaration has been submitted;

b. the mutant holotoxin enhances the immune response in a vertebrate host to said antigen.

10. It is the position of the examiner that the Declaration was not found to be effective and while functional limitations define the claimed compositions for a specific purpose and capability, they do not define the overall structure of the claimed mutant cholera holotoxin. The claims still do not clearly/distinctly claim Applicant's invention.

11. Applicant states that the term "substitution " is causing unnecessary confusion in the Examiner's interpretation of the meaning of the claim.

12. It is the position of the examiner that what is now claimed is a mutant holotoxin of cholera toxin which does not have either glutamic acid or aspartic acid at a corresponding position of the native wild type cholera holotoxin, position 29, but how many mutations, or where or what the mutations are, are not clearly nor distinctly claimed. Claim 15 recites the phase "at least one additional mutation" and depends from claim 1; there is no upper limit to the number or type of mutations that can be introduced into the claimed holotoxin.

13. At page 11, of Applicant's remarks, Applicant states that the examiner points to several sections of the Specification to discuss gene modification of non-coding regions, and states that "an existing promoter is substituted for another promoter in the non-coding region."

14. It is the position of the examiner that the prior Office Action did not discuss gene promoters, nor non-coding regions of genes. At page 6, the examiner discussed leader sequences, which are amino acid sequences that are encoded by coding regions of a gene, not

non-coding regions. Applicant's traversal does not address the issues raised in the last Office Action that sought to show that the instant Specification produced mutant cholera holotoxins that evidenced mutations that were not defined by any specific amino acid sequence (chimeric holotoxin, combination of amino acids from two strains, 569B and 2125, described at page 35, lines 25-33 of the instant Specification). The mutants evidenced changes in the amino acid sequence of the holotoxin, what the changes were, were not specifically described, nor defined.

15. Applicant traverses the rejection under 35 USC 112, second paragraph by asserting the claim language to be clear by stating "that the mutant cholera holotoxin has "an amino acid which replaces the deleted glutamic acid which naturally occurs at position 29 of the mature A subunit".

16. The process claim limitations define a product by process composition, the mutant composition comprises an amino acid that is not glutamic acid nor aspartic acid at position 29 that would normally exist in the wild-type cholera holotoxin. The process limitations do not define a composition that comprises any specific number of mutations, and may be produced by any other process that results in a holotoxin that does not comprise a glutamic acid nor aspartic acid at position 29, but has adjuvanting activity. The claimed invention is claimed based upon *what it is not*, rather than what it is, with respect to position 29; and the rest of the holotoxin mutant structure is not clearly nor distinctly claimed. The rejection of the claims under 35 USC 112, second paragraph is maintained.

17. Applicant asserts that the term "holotoxin" defines a "full-length, biologically functional cholera holotoxin".

18. It is the position of the examiner that what is claimed is a mutant holotoxin, not a wild-type holotoxin. The biological functions required are adjuvanting activity and reduced toxicity. Reduced toxicity results from reduced biological activity, and reduced biological activity includes complete lack of enzymatic biological activity which causes the toxicity of the wild-type cholera holotoxin. Applicant's assertion that the mutant holotoxins of the claimed compositions are all full length, biologically functional cholera holotoxins is not commensurate in scope with the instantly claimed invention.

19. Traversal is made with respect to enablement issues: being able to locate the naturally occurring Glu at position 29 in the A subunit of the wild-type cholera holotoxin variants, and the biological activity can be determined based upon cell based assays.

20. It is the position of the examiner, that the rejection made of record was under 35 USC 112, second paragraph, and not 35 USC 112, first paragraph. The claimed invention is unclear. The term "holotoxin" defines the starting material from which the mutant cholera holotoxin is made. What the mutant holotoxin is, is not clearly nor distinctly claimed.

21. The rejection of claims 1-2, 4, 6-8,11, 13-17, 28, 30,32-34, 37, 39-43 under 35 U.S.C. 102(b) as being anticipated by WO95/17211 (as evidenced by sequence for cholera toxin and E.coli heat labile enterotoxin provided by Zhang et al (1995, page 564, Figure 1)), is traversed on the grounds that Rappuoli does not mention a mutation of position 29 of a mutant cholera holotoxin.

22. It is the position of the examiner that while Rappuoli does not mention position 29, a mutation at position 7, through deletion of the amino acid at position 7(see claim 4) produces a product that results in the amino acid at position 29 that is neither glutamic acid, nor aspartic acid. While Rappuoli produced a product that reads on the instantly claimed invention, by a different process, the compositions of Rappuoli are the same or equivalent products now claimed, which are mutant holotoxins with adjuvant activity, reduced toxicity and are combined with an antigen, wherein the amino acid at position 29 that is neither glutamic acid, nor aspartic acid. The prior art rejection is maintained for reasons of record.

23. The rejection of claims 1, 2, 13 under 35 U.S.C. 102(b) as being anticipated by Glineur et al (1994) is traversed on the grounds that Glineur does not teach an antigenic composition that contains a first antigen and a mutant cholera holotoxin that has an adjuvant effect on the first antigen.

24. It is the position of the examiner that the antigen may be any antigen, and Glineur discloses a strain of Vibrio cholerae 569B-NT that is an antigen, as well as ampicillin resistance, which is also another type of antigen. The mutant holotoxin has tyrosine at amino acid position 29, and does not comprise either glutamic acid, nor aspartic acid at position 29 of the alpha subunit. The functional characteristics of the mutant holotoxin is an inherent characteristic as the mutant holotoxin or the prior art meets all of the structural and functional characteristics now claimed.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594
2. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a

scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. AThe Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art≅.

Conclusion

25. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
May 15, 2006

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